DETAILED ACTION

Applicants' arguments, discussed during the interview dated 14 May 2008, have been fully considered and are deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synergistic effect of L-chicoric acid in combination with zidovudine, dideoxycytidine, or 2',3'-dideoxyinosine when used to treat the two HIV strains, $HIV_{NL4\text{-}3\ M185V}$ and $HIV_{NL4\text{-}3\ JF26/A7}$, does not reasonably provide enablement for the broader synergistic therapeutic effect of reverse transcriptase inhibitors in combination with integrase inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue

experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, all Wands factors have been considered and the following factors that are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to treatment of disease, particularly the synergistic effect when treating patients with HIV resistant to treatment by reverse transcriptase inhibitor. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. Synergism by definition is an unexpected result greater than addition. The court has held that a limited number of examples of compositions with synergistic effects do not support the broader genus of compositions. *In re Kollman*, 201 USPQ 193 (C.C.P.A. 1979).

2. The breadth of the claims

The claim relates to synergistic effect resulting from the combination of two distinct classes of drugs and is therefore quite broad.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for synergistic effect of the many possible combinations. No reasonably specific guidance is provided concerning useful picking compounds with synergistic effect, other than the synergistic effect of L-chicoric acid in combination with zidovudine, dideoxycytidine, or 2',3'-dideoxyinosine when used to treat the two HIV strains, $HIV_{NL4-3\ M185V}$ and $HIV_{NL4-3\ JF26/A7}$ at the specific concentrations disclosed. The latter is corroborated by the working examples.

As explained above, only the three instantly disclosed combinations to treat the two strains at the disclosed concentrations can be considered to be synergistic and therefore do not provide sufficient basis to expect synergism for the broader combinations.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably produce synergistic therapeutic results when treating a patient having an HIV infection that is at least partially resistant to treatment by reverse transcriptase inhibitor. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dombrowaki et al (US 5,759,842 filed 24 Oct 1996 and issued 2 June 1998) in view of Bell (US 5,663,161, filed 2/17/1995 and issued 10/2/1997).

Dombrowaki et al teaches treatment of HIV patients with a combination of HIV integrase inhibitors and the reverse transcriptase inhibitor zidovudine (column 8 lines 36-44 and column 9 lines 10-11).

Dombrowaki et al does not teach administration to HIV strains resistant to AZT or disclose the other reverse transcriptase inhibitors, ddI or ddC.

Bell teaches treating HIV strains resistant to AZT at different stages in the HIV life cycle (column 1 line 19-34). Specifically, an integrase inhibitor can be used in combination with reverse transcriptase inhibitors (column 23 lines 42-64), where AZT, ddI and ddC are previously known reverse transcriptase inhibitors (column 1 lines 24-26).

It would be obvious to one of ordinary skill in the art to use the compounds of the primary reference, or other known reverse transcriptase inhibitors as disclosed in the secondary reference, in combination as taught by the secondary reference.

With regards to the synergy, the question at issue of *In re Kollman* is whether a limited number of synergistic results are insufficient to overcome a proper 103 prima facia case directed to a genus of compounds (note, the claims at issue in *In re Kollman* specifically included the limitation of "synergistic"). The court held that a limited number of combinations were not sufficient to overcome a 103 rejection which obviated combinations outside the limited synergistic combinations, even though the 103 rejection did not teach unexpected results.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-F 8-3:45 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Patent Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612